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A multicenter trial of oxcarbazepine oral suspension monotherapy in children newly diagnosed with partial seizures: A clinical and cognitive evaluation

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ABSTRACT

Purpose: We conducted a prospective, multicenter, open label trial to evaluate the effectiveness of oxcarbazepine (OXC) oral suspension as monotherapy for children newly diagnosed with partial seizures.
Methods: This trial included a two- to eight-week titration and stabilization period to achieve effective target doses and a 24-week maintenance phase. The primary outcome measure was the seizure-free rate over six months, while a secondary measure was the change in cognition and behavior from screening to the end of the maintenance phase. The effectiveness of OXC was compared in intellectually normal versus intellectually impaired children (intelligence quotient <70).
Results: We enrolled 171 patients and analyzed 168 as the per-protocol (PP) group (3 patients had protocol violations). The mean age of the PP group was 8.4 ± 2.7 years. The maintenance dose of OXC was 24.9 ± 8.0 mg/kg/day. Of the 168 patients included in the efficacy analysis, 122 (72.6%) completed the study and 94 (56.0%) became seizure-free after the OXC treatment. Comparing the efficacy of OXC for intellectually normal and intellectually impaired patients, 79 (56.8%) of the 139 intellectually normal patients and 15 (51.7%) of the 29 intellectually impaired patients became seizure-free ($P = 0.61$). After treatment, intelligence scale scores improved in intellectually normal patients compared to the intellectually impaired children ($P < 0.05$). Social problems quantified by behavior scales improved in intellectually impaired patients compared to intellectually normal children ($P < 0.05$).
Conclusions: OXC is effective and well-tolerated as monotherapy in children with partial seizures. There was no difference in the effectiveness of OXC between intellectually normal and intellectually impaired children.

1. Introduction

Oxcarbazepine (OXC) is an antiepileptic drug (AED) that is chemically related to carbamazepine and is approved for the initial or add-on treatment of partial seizures.[1] OXC is also one of the first-line AEDs used for the treatment of partial seizures in children. However, only a few studies have prospectively evaluated OXC as a primary monotherapy in children with newly diagnosed epilepsy. Both cognitive and behavioral effects are key considerations in the selection of AEDs because of the influence of these parameters on the acquisition of new skills and the ability to develop social strategies at crucial stages of development. In this study, we evaluated the efficacy and tolerability of OXC as monotherapy for seizure control, including an analysis of neuropsychological effects, in children less than 16 years of age with newly diagnosed epilepsy. We also compared the effectiveness of OXC in intellectually normal children and intellectually impaired children.

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2. Methods

2.1. Subjects

Children less than 16 years of age were eligible for the study if they had been diagnosed with epilepsy and had experienced two or more unprovoked partial seizures within the previous six months. Exclusion criteria included evidence of a progressive cerebral lesion or a neurodegenerative metabolic disorder as well as a history of psychiatric disorder. Patients previously treated with AEDs were also excluded. Epilepsy was classified as symptomatic, cryptogenic, or idiopathic, in the following manner: symptomatic epilepsy was diagnosed if a structural brain disorder was identified based on abnormal results of the magnetic resonance imaging (MRI) scan; cryptogenic epilepsy was diagnosed if recurrent partial seizures were present despite normal MRI scan results; and a diagnosis of idiopathic epilepsy was made when no underlying structural brain or metabolic abnormality could be identified based on normal results of the diagnostic tests, and a genetic predisposition was suspected (i.e. benign rolandic epilepsy and benign occipital epilepsy).

The study was conducted at ten referral hospitals for pediatric epilepsy care and its protocol was approved by the institutional review boards of all of the participating centers. Informed consent was obtained from all participants as well as their guardians before any trial-related procedures were performed.

2.2. Study design

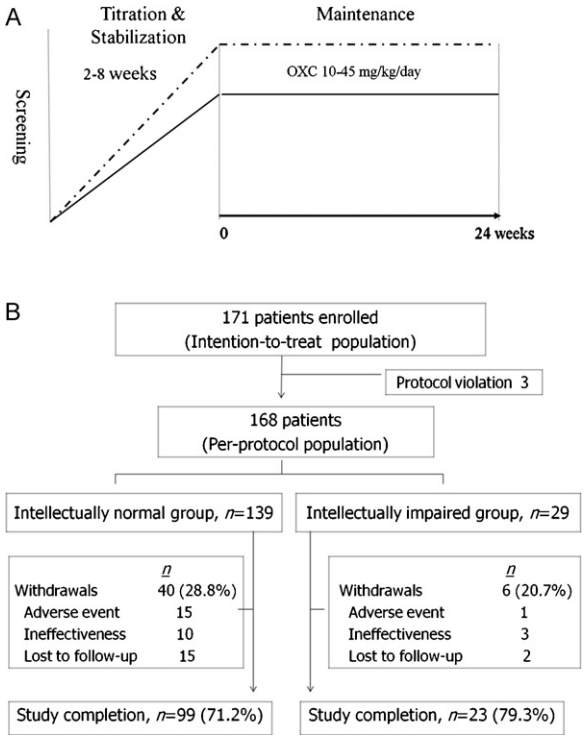

Fig. 1. (A) Trial design; (B) trial progression.

The study was an open-labeled, multicenter clinical trial for OXC monotherapy in children with partial seizures. The study included a retrospective baseline phase of six months and a screening phase of one week during which eligibility was determined and all screening procedures were carried out. The 26- to 32-week treatment periods included an initial titration and stabilization phase of 2–8 weeks and a maintenance period of 24 weeks. Before starting medication, all subjects were evaluated for their intelligence, behavior, and quality of life at baseline. OXC was introduced at 5–10 mg/kg daily and increased by 5–10 mg/kg/day every one to two weeks. The maintenance dose for OXC was 20–30 mg/kg/day. Blood levels of OXC were not measured. If the seizure frequency or intensity increased compared to that of baseline, the dose was increased gradually up to an effective and tolerable dose. If, however, maintenance of OXC was rendered difficult due to adverse effects during titration or within eight weeks of reaching the maintenance dose, the dose was then gradually reduced (Fig. 1A).

2.3. Outcome measures

Throughout the trial, patients (or their parents or legal guardians) maintained diaries to record the types and frequencies of seizures as well as adverse effects. At each hospital visit, the investigator reviewed the patient's seizure diary. Patient visits were scheduled for visits on day 1 (screening) and then in weeks 4, 8, 12 and 20, and once during weeks 24–28.

The primary efficacy endpoint was the seizure-free rate during the maintenance period, while secondary efficacy endpoints included changes in cognition and behavior in a combined analysis of standardized measures from the screening period to the end of the maintenance phase. Comprehensive neuropsychological tests were carried out during the screening period (up to 7 days before the start of the titration) as well as at the end of the study (28 weeks). The Korean Wechsler Intelligence Scale for Children-Third Edition (K-WISC-III) was used for cognitive assessment. The K-WISC-III comprises a full scale intelligence quotient (IQ), verbal IQ, and performance IQ with 13 subtests: information, similarities, arithmetic, vocabulary, comprehension, digit span, picture completion, picture arrangement, block design, object assembly, coding, mazes and symbol search. Verbal IQ is based on information, similarities, arithmetic, vocabulary and comprehension. The performance IQ is based on picture completion, coding, picture arrangement, block design and object assembly. An integrated cognitive function index was obtained with the results of the K-WISC-III as follows: (1) verbal comprehension index: information, similarities, vocabulary and comprehension; (2) perceptual organization index: picture completion, picture arrangement, block design and object assembly; (3) freedom from distractibility index: arithmetic and digit span; and (4) processing speed index: coding and symbol search.

To measure the extent of behavioral problems, the Korean child behavior checklist (K-CBCL) was used. The K-CBCL is divided into social competence and behavioral problem analysis, with the former providing assessments of total social competence, school and social problems, and the latter providing one score for total behavioral problems, two second-order factor scores for internalizing and externalizing problems, and eight syndrome scales for assessing aggressive behavior, anxious/depressed, delinquent behavior, attention problems, social problems, thought problems, and withdrawn and somatic complaints. The *T*-scores of these 14 subscales of the K-CBCL were used in the analysis. The Korean Quality of Life Survey for Childhood Epilepsy (K-QOLCE) consists of a 42-item scale that assesses well-being, social activity, physical activity, cognitive functioning, behavioral functioning, general health and overall quality of life within the previous four weeks. The overall quality-of-life scoring scale ranges from 0 to 100, with higher scores representing better quality of life.

The tolerability and safety of OXC were monitored throughout the trial by neurological and physical examinations that took into account patient weight, vital signs and an evaluation of treatment-related adverse effects (one visit during the baseline period followed by five subsequent visits during the 28-week trial). Clinical laboratory assessments (hematology, blood chemistry, and

urinalysis) were also performed at baseline, after four weeks of treatment, and at the end of the study. The incidence of treatment-related adverse effects was compared between intellectually normal and intellectually impaired children.

2.4. Statistical methods

For analysis of the seizure-free rate during the treatment period, which was the primary efficacy parameter of interest, the intention-to-treat (ITT) population included all patients who enrolled in this study and received at least one dose of OXC. The per-protocol (PP) population for efficacy analyses included all ITT patients who received at least one dose of OXC and provided at least one on-treatment efficacy evaluation, while patients with at least one protocol violation were excluded. A chi-squared test was used to compare seizure outcomes between the intellectually normal and intellectually impaired children. The data from neuropsychological tests are summarized as means with standard deviations (SDs) or as numbers (percentages). A paired Student's *t*-test across the neuropsychological variables was used to compare changes over time for each treatment group. Mean changes over time between groups were compared using the Student's *t*-test. All reported *P*-values were two-tailed and *P*-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Subject characteristics and distribution

The ITT population included 171 subjects, consisting of 99 boys and 72 girls, with a mean age of 8.9 ± 2.7 (range, 3–15) years. After accounting for the 3 patients with protocol violations, 168 subjects were analyzed as the PP group, which consisted of 98 boys and 70 girls with a mean age of 8.4 ± 2.7 (range, 3–15) years. Epilepsy was classified as symptomatic, cryptogenic, or idiopathic, the latter group composed of 60 cases of benign rolandic epilepsy and 3 cases of benign occipital epilepsy. The known causes of symptomatic epilepsy were encephalomalacia (3 patients, 1.8%), brain atrophy (3, 1.8%), brain malformation (3, 1.8%), hippocampal sclerosis (3, 1.8%), brain tumor (1, 0.6%), and stroke (1, 0.6%). The two groups (intellectually normal and intellectually impaired patients) were similar with regard to gender and age (Table 1). Of the 139 intellectually normal patients in the PP population, consisting of 79 boys and 60 girls, there were 63 patients (36 boys, 27 girls) with idiopathic epilepsy and 76 patients (44 boys, 32 girls) with cryptogenic/symptomatic epilepsy. All 29 intellectually impaired children (19 boys and 10 girls) had cryptogenic/symptomatic forms of epilepsy. Etiological differences were apparent between the intellectually normal and intellectually impaired patient groups ($P < 0.001$).

Table 1
Baseline characteristics of study patients in the per-protocol population.

	Intelligence		*P*-value
	Normal ($n = 139$)	Impaired ($n = 29$)	
Age (years), mean ± SD	8.26 ± 2.55	8.86 ± 3.26	0.728[a]
Male:female ratio	79:60	19:10	1.0[b]
Epilepsy classification and etiology, *n* (%)			<0.001[b]
Idiopathic	63 (45.3%)		
Cryptogenic	70 (50.4%)	20 (69.0%)	
Symptomatic	6 (4.3%)	9 (31.0%)	

[a] Student's *t*-test.
[b] Fisher's exact test.

Fig. 1A and B describes the study design and the distribution, respectively, of subjects following enrollment. Among the 168 PP patients, 46 patients (27.4%) did not complete the study due to drug ineffectiveness (13 patients, 7.7%), loss to follow-up (17, 10.1%), or adverse effects (16, 9.5%). Among the 13 patients who experienced drug ineffectiveness, two had idiopathic epilepsy and 11 had cryptogenic/symptomatic forms of epilepsy. Adverse effects that resulted in drug discontinuation were all associated with skin rashes that occurred after OXC treatment was started.

3.2. Efficacy analysis for seizure-free rate during six months of maintenance

Seventy-nine patients (56.8%) in the intellectually normal group and 15 (51.7%) in the intellectually impaired group fulfilled the primary objective of six months of freedom from seizures ($P = 0.614$). Table 2 shows the seizure-free rate according to etiology for the 24 weeks of the maintenance period. Among the 63 patients with idiopathic epilepsy, 42 patients (66.7%) became seizure-free, while 44 (48.9%) of 90 patients with cryptogenic epilepsy and 8 (53.3%) of 15 patients with symptomatic epilepsy became seizure-free. Overall, seizure-free rates during the maintenance period were not different between groups according to etiology ($P = 0.614$ for all partial epilepsy; $P = 0.535$ for cryptogenic epilepsy; $P = 0.608$ for symptomatic epilepsy).

3.3. Neuropsychological assessments

3.3.1. Cognition

Results of the comparison of baseline-to-endpoint changes between the intellectually normal and intellectually impaired groups are summarized in Tables 3 and 4. Neuropsychological data for cognitive variables were available for 113 patients (97 in the intellectually normal and 16 in the intellectually impaired group). After treatment, the perceptual organization, attention and concentration, and picture completion subtests were improved in the intellectually normal group ($P < 0.05$). A comparison of the intellectually normal and impaired groups showed that results for the information subtest in the intellectually impaired group were significantly worse than that in the intellectually normal group ($P = 0.008$) (Table 3).

3.3.2. Behavior

Neuropsychological data for behavioral variables were provided by 108 patients (93 in the intellectually normal group and 15 in the intellectually impaired group). In the intellectually normal group, depression/anxiety ($P = 0.010$), thought problems ($P = 0.034$), delinquent behavior ($P = 0.016$), and overall behavioral problems ($P = 0.035$) were improved after treatment, while in the intellectually impaired group, somatic complaints ($P = 0.021$), depression/anxiety ($P = 0.013$), social problems ($P = 0.022$), internalizing problems ($P = 0.007$), and overall behavioral problems ($P = 0.025$) were improved after treatment. A comparison of the intellectually normal and impaired groups showed that the status

Table 2
Seizure-free state for 24 weeks according to epilepsy type in the per-protocol population.

Epilepsy classification	Intellectually normal	Intellectually impaired	*P*-value
Partial epilepsy	79/139 (56.8%)	15/29 (51.7%)	0.614[a]
Idiopathic	42/63 (66.7%)	–	–
Cryptogenic	33/70 (47.1%)	11/20 (55.0%)	0.535[a]
Symptomatic	4/6 (66.7%)	4/9 (44.4%)	0.608[b]

[a] Chi-squared test.
[b] Fisher's exact test.

Table 3
Cognition changes after OXC treatment in the per-protocol population.

Intelligence (K-WISC-III)	Intellectually normal (n = 97)			Intellectually impaired (n = 16)			Intellectually normal vs. impaired
	Baseline (SD)	Change from baseline (SD)	P-value[a]	Baseline (SD)	Change from baseline (SD)	P-value[a]	P-value[b]
Full scale IQ	97.68 (15.68)	1.268 (9.90)↑	0.210	44.88 (12.48)	0.250 (4.98)↑	0.844	0.577
Verbal IQ	98.57 (15.04)	0.622 (9.14)↑	0.502	52.47 (14.28)	−0.733 (5.93)↓	0.640	0.407
Performance IQ	97.06 (15.66)	2.268 (13.24)↑	0.095	47.19 (13.17)	0.375 (5.22)↑	0.778	0.508
Verbal comprehension	98.57 (15.16)	1.012 (9.00)↑	0.312	51.64 (13.51)	0.143 (6.79)↑	0.938	0.769
Perceptual organization	96.53 (14.82)	3.506 (11.61)↑	0.008	47.86 (12.94)	0.786 (3.01)↑	0.348	0.390
Attention and concentration	95.74 (16.23)	2.695 (11.98)↑	0.045	53.43 (16.36)	0.000 (8.86)	1.000	0.291
Processing speed	99.30 (14.48)	0.463 (14.83)↑	0.781	60.14 (12.82)	−0.853 (5.85)↓	0.593	0.310
Information	9.98 (3.18)	0.020 (1.96)↑	0.918	3.06 (2.01)	−0.438 (1.45)↓	0.249	0.008
Similarities	10.70 (3.12)	0.398 (2.31)↑	0.091	3.75 (2.40)	0.313 (2.27)↑	0.590	0.085
Arithmetic	9.58 (2.91)	0.061 (2.46)↑	0.806	2.69 (2.44)	−0.250 (1.23)↓	0.432	0.556
Vocabulary	9.93 (2.99)	0.000 (2.54)	1.000	3.00 (2.55)	0.188 (2.07)↑	0.723	0.095
Comprehension	9.34 (2.61)	−0.255 (2.78)↓	0.367	2.69 (2.52)	−0.375 (1.36)↓	0.287	0.883
Digit span	9.37 (3.01)	0.402 (2.06)↑	0.081	2.71 (2.61)	0.286 (1.93)↑	0.591	0.627
Picture completion	9.33 (2.64).	0.567 (2.70)↑	0.042	2.88 (2.15)	0.313 (1.07)↑	0.264	0.770
Picture arrangement	9.48 (2.67)	0.704 (3.22)↑	0.053	2.50 (1.78)	0.071 (1.54)↑	0.865	0.637
Block design	9.93 (3.02)	−0.031 (2.25)↓	0.893	2.56 (1.78)	−0.125 (1.08)↓	0.652	0.272
Picture assembly	9.46 (2.69)	0.351 (2.89)↑	0.236	3.44 (2.36)	−0.25 (1.91)↓	0.609	0.430
Coding	9.46 (2.62)	0.333 (2.98)↑	0.318	2.64 (1.73)	0.071 (1.85)↑	0.888	0.466

↑ and ↓ indicate a trend toward improvement or deterioration, respectively. OXC, oxcarbazepine; K-WISC-III, Korean Wechsler Intelligence Scale for Children-Third Edition; IQ, intelligence quotient.
[a] Paired Student's t-tests for changes from baseline.
[b] Student's t-test for comparing changes from baseline between the intellectually normal and intellectually impaired groups.

of social problems improved more in the intellectually impaired group than in the intellectually normal group (P = 0.011) (Table 4).

3.3.3. Quality of life

Neuropsychological data concerning quality of life were obtained from 97 patients (83 in the intellectually normal group and 14 in the intellectually impaired group). In the intellectually normal group, memory was improved after treatment (P = 0.029), but there were no significant differences in memory improvement between the two groups (P = 0.493). Overall, the change in quality of life did not vary significantly between the groups (Table 5).

3.4. Adverse effects

There were several drug-related adverse effects (Table 6), but rash was the only reason that led to withdrawal from the study during the titration and maintenance period. Rashes developed 6–30 days after the start of OXC medication in 30 patients (17.9%). Of these, rashes in 28 patients (16.7%) were assessed as probably related to OXC use, while the underlying cause was viral illnesses in the other 2 patients. OXC-related rashes with mild diffuse erythematous maculopapules or bullous eruptions with/without itching presented mainly on the trunk and face. There was associated fever in 2 patients, but no evidence was seen of Stevens–Johnsons syndrome (SJS) or toxic epidermal necrolysis. The starting daily dose of OXC was 9.0 ± 4.6 mg in patients with rashes and 9.5 ± 4.6 mg in patients without (P = 0.686). OXC was increased once per week such that the overall daily dose was raised by 5–10 mg/kg. Fifteen patients (10.8%) in the intellectually normal group and one patient (3.4%) in the intellectually impaired group withdrew from the study due to the appearance of a rash (P = 0.311). There were no serious adverse effects reported during the study period.

4. Discussion

The purpose of this study was to evaluate the efficacy of OXC monotherapy for seizure control and tolerability in children. The results showed that OXC as monotherapy produced a 56.0%

Table 4
Behavioral changes after OXC treatment in the per-protocol population.

Behavior (K-CBCL)	Intellectually normal (n = 93)			Intellectually impaired (n = 15)			Intellectually normal vs. impaired
	Baseline (SD)	Change from baseline (SD)	P-value[a]	Baseline (SD)	Change from baseline (SD)	P-value[a]	P-value[b]
Social competence	51.99 (13.53)	2.65 (13.65)↑	0.066	40.40 (13.66)	1.00 (12.29)↑	0.757	0.666
School competence	46.34 (19.76)	3.09 (18.33)↑	0.108	34.20 (11.00)	2.27 (11.54)↑	0.460	0.574
Total social competence	46.53 (19.52)	3.26 (18.49)↑	0.094	32.33 (13.87)	3.20 (11.39)↑	0.295	0.272
Withdrawn	50.38 (12.37)	−2.16 (15.00)↑	0.168	55.07 (6.45)	−2.80 (8.03)↑	0.198	0.595
Somatic complaints	51.65 (8.17)	−1.12 (8.82)↑	0.225	50.80 (7.68)	−3.93 (5.89)↑	0.021	0.174
Depression/anxiety	49.17 (8.75)	−2.22 (8.14)↑	0.010	51.80 (5.91)	−4.93 (6.69)↑	0.013	0.128
Social problems	48.68 (8.39)	0.28 (8.94)↓	0.762	66.93 (8.53)	−7.93 (11.95)↑	0.022	0.011
Thought problems	49.95 (6.56)	−1.61 (7.17)↑	0.034	53.80 (10.20)	−4.53 (9.57)↑	0.088	0.250
Attention problems	48.44 (8.99)	−0.871 (8.89)↑	0.347	59.27 (7.70)	−5.40 (9.93)↑	0.054	0.086
Delinquent behavior	48.35 (7.04)	−1.53 (6.01)↑	0.016	49.67 (6.26)	−1.73 (10.45)↑	0.531	0.925
Aggressive behavior	47.18 (8.43)	−1.25 (7.75)↑	0.124	50.67 (8.31)	−2.40 (6.31)↑	0.163	0.587
Internalizing problems	49.59 (8.32)	−1.63 (8.44)↑	0.065	52.80 (6.00)	−4.60 (5.64)↑	0.007	0.135
Externalizing problems	47.31 (8.15)	−1.47 (7.19)↑	0.051	50.20 (7.74)	−2.07 (7.12)↑	0.280	0.799
Overall behavioral problems	47.84 (8.17)	−1.74 (7.85)↑	0.035	55.87 (5.33)	−5.67 (8.73)↑	0.025	0.114

↑ and ↓ indicate a trend toward improvement or deterioration, respectively. OXC, oxcarbazepine; K-CBCL, Korean Child Behavior Checklist.
[a] Paired Student's t-tests for changes from baseline.
[b] Student's t-test for comparing changes from baseline between the intellectually normal and intellectually impaired groups.

Table 5
Changes in quality of life after OXC treatment in the per-protocol population.

K-QOLCE		Intellectually normal (n = 83)			Intellectually impaired (n = 14)			Intellectually normal vs. impaired
		Baseline (SD)	Change from baseline (SD)	P-value[a]	Baseline (SD)	Change from baseline (SD)	P-value[a]	P-value[b]
Physical function	Physical restriction	392.47 (92.95)	−21.39 (99.93)↓	0.055	275.00 (106.97)	12.50 (85.91)↑	0.959	0.972
	Energy/fatigue	146.69 (35.52)	1.09 (39.00)↑	0.674	117.86 (43.22)	−1.79 (34.62)↓	0.850	0.543
Well-being (mood)	Depression	40.66 (30.92)	1.51 (29.30)↑	0.641	55.36 (32.79)	1.79 (18.25)↑	0.720	0.838
	Anxiety	224.10 (73.01)	−6.63 (94.68)↓	0.526	187.50 (47.79)	19.64 (85.58)↑	0.406	0.397
	Control/helplessness	153.31 (56.68)	−1.51 (63.72)↓	0.830	128.57 (29.18)	12.50 (55.25)↑	0.413	0.883
	Self-esteem	219.58 (53.11)	−1.80 (48.42)↓	0.735	160.71 (61.79)	0.00 (50.0)	1.000	0.588
Cognition	Concentration	153.01 (51.56)	0.60 (61.60)↑	0.929	98.21 (39.79)	−1.79 (55.87)↓	0.907	0.532
	Memory	157.23 (44.94)	12.65 (51.70)↑	0.029	132.14 (50.41)	10.71 (47.75)↑	0.416	0.493
	Language	282.23 (270.54)	22.89 (281.52)↑	0.461	141.07 (76.97)	−14.29 (53.45)↓	0.336	0.206
	Other	154.22 (47.47)	−3.61 (45.05)↓	0.467	82.14 (49.45)	−7.13 (3.66)↓	0.414	0.644
Social function	Social activities	226.81 (62.93)	1.81 (86.93)↑	0.850	175.00 (75.96)	−14.29 (76.40)↓	0.497	0.294
	Social interactions	168.07 (49.44)	6.02 (60.06)↑	0.363	117.86 (71.68)	16.07 (78.81)↑	0.459	0.805
General	Behaviors	561.14 (129.57)	−22.29 (154.11)↓	0.101	475.00 (90.94)	−1.79 (66.84)↓	0.349	0.862
	Health	60.84 (37.89)	−0.90 (42.31)↓	0.337	48.21 (33.20)	−8.93 (33.40)↓	0.336	0.347
	Quality of life	57.83 (36.40)	−4.22 (39.78)↓	0.337	51.79 (35.98)	3.57 (46.89)↑	0.780	0.484
Total		2998.19 (595.85)	−15.06 (655.32)	0.835	2246.43 (429.99)	28.79 (255.98)↑	0.702	0.561

↑ and ↓ indicate a trend toward improvement or deterioration, respectively. OXC, oxcarbazepine; K-QOLCE, Korean Quality of Life Survey for Childhood Epilepsy.
[a] Paired Student's t-tests for changes from baseline.
[b] Student's t-test for comparing changes from baseline between the intellectually normal and intellectually impaired groups.

seizure-free rate in childhood partial epilepsy and that the efficacy for seizure control was not different between intellectually normal and intellectually impaired children. Moreover, there was no difference in treatment efficacy in relation to the etiology of the childhood partial epilepsy. OXC was also beneficial in several subsets of cognition and behavior, such as perceptual organization and depression/anxiety.

Previous studies investigating OXC have mostly addressed its adequacy as an add-on therapy in intractable epilepsy patients.[2–4] Other studies have also focused mainly on retrospective analyses through chart review,[5,6] while more recent reports describe the study of the effects of OXC monotherapy in small numbers of children and young adults via prospective observation.[7–11] In contrast, the present study was conducted on 168 patients with newly diagnosed, untreated pediatric partial epilepsy (less than 16 years of age) to evaluate the seizure-controlling effects of OXC as a first-line therapy and to address its safety and adverse effects, including its effects on cognitive functions and behavior. Our results show that OXC can be used effectively without causing serious systemic adverse effects. The efficacy of OXC for seizure control did not differ between intellectually normal and intellectually impaired children.

The underlying cause of epilepsy is a major determinant of treatment, prognosis and clinical course. It has been generally acknowledged that idiopathic epilepsy responds better to AEDs than does symptomatic epilepsy; however, our results indicate that there were no differences in OXC efficacy among the various groups according to the etiology (idiopathic, cryptogenic, and symptomatic) of the epilepsy.

In relation to cognition, this study showed that perceptual organization, attention and concentration, and picture completion subtests were only improved after treatment in the intellectually normal group. A particularly interesting finding here was that although a follow-up evaluation after a six-month interval may have influenced these learning effects, the improvements were only observed in the intellectually normal group. Moreover, the result of the information subtest in the intellectually impaired group was significantly poorer than that in the intellectually normal group. This finding shows that changes in cognition after AED treatment relate to baseline cognitive ability prior to treatment. Although a randomized head-to-head comparison is required to compare the neurobehavioral effects of AEDs, the results of this study suggest that OXC could be beneficial to treat children without risking the possible manifestation of problems associated with language development that are seen after treatment with topiramate or zonisamide.[12–15] An analysis of behavioral changes after OXC treatment showed that OXC was beneficial in relation to several aspects of behavior. In particular, the social problem parameter in intellectually impaired children improved significantly compared with that of intellectually normal children.

With respect to drug-related adverse effects, the occurrence of rash was the only cause for drug withdrawal; these rashes completely resolved after drug discontinuation. The U.S. Food and Drug Administration recommends screening for the human leukocyte antigen (HLA)-B*1502 allele in people of Asian ancestry before initiating carbamazepine therapy and a recently published paper reporting HLA genotypes in Koreans showed that HLA-B*1511 and A*3101 were associated with carbamazepine-induced SJS and hypersensitivity syndrome/severe cutaneous adverse

Table 6
Frequencies of adverse effects.

	Intellectually normal (n = 139)	Intellectually impaired (n = 29)
Rash	25 (17.9%)[a]	5 (17.2%)[b]
Headache	8 (5.8%)	1 (3.4%)
Somnolence	4 (2.9%)	1 (3.4%)
Dizziness	3 (2.2%)	2 (6.9%)
Fatigue	2 (1.4%)	3 (10.3%)
Anxiety	1 (0.7%)	2 (6.9%)
Ataxia	0	1 (3.4%)
Memory loss	1 (0.7%)	1 (1.6%)
Paresthesia	1 (0.7%)	0
Weight gain	2 (1.4%)	0
Weight loss	1 (0.7%)	0
Epigastric pain	1 (0.7%)	0
Hyponatremia	1 (0.7%)	0

[a] Fifteen patients in the intellectually normal group.
[b] One patient in the intellectually impaired group withdrew because of adverse effects.

reaction, respectively, in the Korean population.[16] We did not analyze HLA genotypes in this study, but the occurrence of rash was not related to the initiation dose or the rapidity of dosage escalation employed here. The evaluation of genetic susceptibility using HLA genotyping would no doubt have proven helpful. There were no other serious problems after OXC administration, which implies that OXC can be used safely in children with epilepsy.

Several limitations to this study should be noted. First, the study design could be improved, as the follow-up period of 6 months is relatively short for the measurement of pragmatic outcomes. Additionally, the short interval between cognitive evaluations may have led to learning effects. Future studies should include a longer follow-up and use more sensitive tools to determine more specific changes, if any, in children's cognition and overall behavior.

In conclusion, OXC is an effective monotherapy for newly diagnosed childhood partial epilepsy. Intellectual ability and the etiology of partial epilepsy are not predictors of OXC responsiveness in pediatric patients.

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